Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1 – 24. (canceled)

25. (currently amended) An *in vitro* method of increasing targeting frequency of a targeting construct in mouse embryonic stem (ES) cells, comprising:

(a) constructing a first targeting vector directed to a specific chromosomal location in a mouse ES cell, wherein the first targeting vector comprises a drug resistance gene ~~driven by~~ operably linked to a PGK promoter;

(b) introducing the first targeting vector into mouse ES cells *in vitro* to obtain a first group of targeted mouse ES cell[[s]] clones;

(c) determining ~~a first targeting efficiency~~ the number of targeted mouse ES cell clones as measured by targeted gene modifications due to targeted, non-random insertions of the first targeting vector in the first group of targeted mouse ES cell[[s]] clones;

(d) constructing a second targeting vector directed to the specific chromosomal location of step (a), wherein the second targeting vector comprises a drug resistance gene ~~driven by~~ operably linked to a ubiquitin promoter;

(e) introducing the second targeting vector into a second group of mouse ES cells *in vitro* to obtain a second group of targeted mouse ES cell[[s]] clones; and,

(f) determining a second ~~targeting efficiency~~ number of targeted mouse ES cell clones as measured by targeted gene modifications due to targeted, non-random insertions of the second targeting vector in the second group of targeted mouse ES cell[[s]] clones, wherein the second targeting ~~efficiency~~ number is proportionately at least two-fold higher than the first targeting ~~efficiency~~ number.

26. (previously presented) The method of claim 25, wherein the ubiquitin promoter is the ubiquitin C promoter.

27. (previously presented) The method of claim 26, wherein the ubiquitin promoter is a human,

mouse, or rat ubiquitin promoter.

28. (previously presented) The method of claim 25, wherein the drug resistance gene encodes neomycin phosphotransferase, hygromycin phosphotransferase, or puromycin acetyl transferase.

29. – 32. (canceled)